Legal and Regulatory Issues in Biotechnology
Prof. Niharika Sahoo Bhattacharya
Rajiv Gandhi School of Intellectual Property Law
Indian Institute of Technology, Kharagpur

Module - 03
Biotech Product commercialization: Regulatory Approval Process
Lecture - 13
Regulatory approval process for Biopharmaceuticals

Hello all, welcome back again. So far, we have seen the regulatory approval process for the genetically modified plants and in today's lecture, I would like to take you through the Regulatory approval process for the Biopharmaceuticals.

So, as we know, these biopharmaceuticals or the products derived by the recombinant DNA process are more complex molecules and it involves the living organisms, and the safety, standard safety purity standards are comparatively higher than the normal chemical drugs and that needs more tests, more different kinds of regulatory requirements to be approved before it comes to the market.

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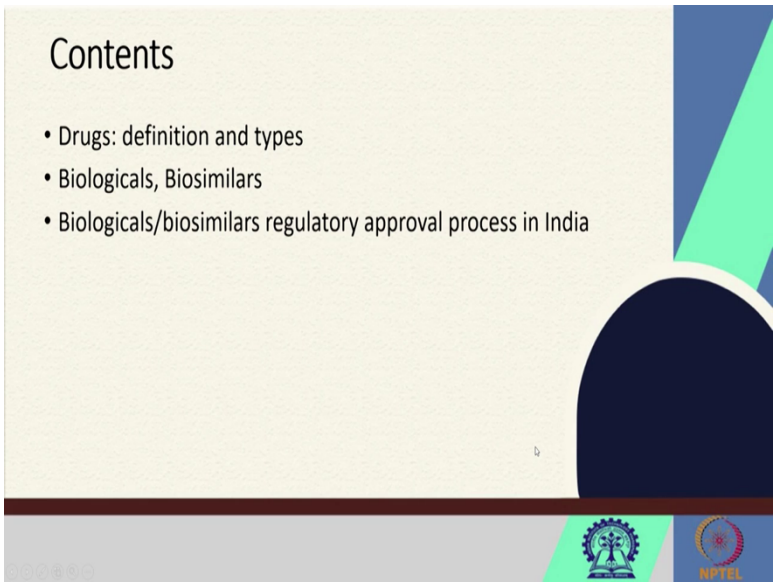

So, in this regard, in this lecture, we will look into the definition and the types of the different drugs as defined in the Drugs and cosmetic Act. Then, we would also like to go into the concept of biologicals or biosimilars and how these biological drugs or the

biosimilar compounds are approved in India. So, this will be the basic structure in which we will go through this lecture.

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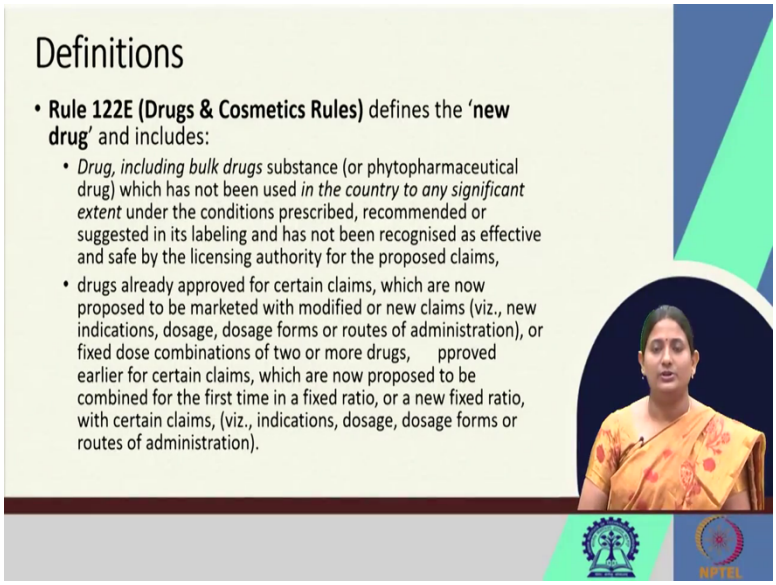

So, before moving into the biopharmaceutical, let us understand how the drug or the pharmaceuticals are defined in India. So, as you know we have a Drugs and Cosmetic Act of 1940 and the corresponding rules.

So, this is the basic legislation which defines the various categories of the drug substances or drug molecule, and it lays down the various provision by which the drug manufacturer has to comply and the regulatory approval procedure through which it can be approved for marketing in India or for import or export from different countries or to different countries.

So, if we see the definition of the 'Drug', the Rule 122E of the drugs and cosmetic Rules defines the new drug as the drug substances including the bulk drug substances, it may be generally derived from the normal chemical synthesis process or it may be derived from a natural source like the plant or phytopharmaceuticals which we generally call.

So, any drug including the bulk drug substance or the phytopharmaceuticals which has not been used in the country to any significant extent under the condition prescribed, recommended or suggested in its labelling and has not been recognized as effective and safe by the licensing authority for the proposed claims.

So, any new substances or any new drug molecule which has certain indication, or which is effective, again certain indication as prescribed by the manufacturer, but it has not been approved anywhere or in our country, then it may come under the category of the new drug molecule. Similarly, not only the new substance which have not been approved so far, but it also includes the drugs which are already approved for certain claims, but now, these drugs are proposed to be marketed with the modified or new claims means new indication.

Earlier, it is used for some disease, now it can be useful for new set of diseases or it can be introduced through new route of administration or it can be introduced in new dosage forms. So, the new use of the already approved drug may also come under the purview of this new drug. So, this is the definition which is given for the new drug molecule in India. So, as you know the recombinant drug development process, or the recombinant DNA technology is a very latest addition.

So, as we know, somewhere after 1970, we have got this techniques and since the Drugs and Cosmetic Act is of 1940 so, at that time, it did not include any provision for the biopharmaceuticals or the recombinant DNA molecules. But later on, when the recombinant DNA molecule had been introduced, then gradually those things has been incorporated into our Drugs and Cosmetic Act. Otherwise broadly it includes everything under this category of the drug as defined in the |Act.

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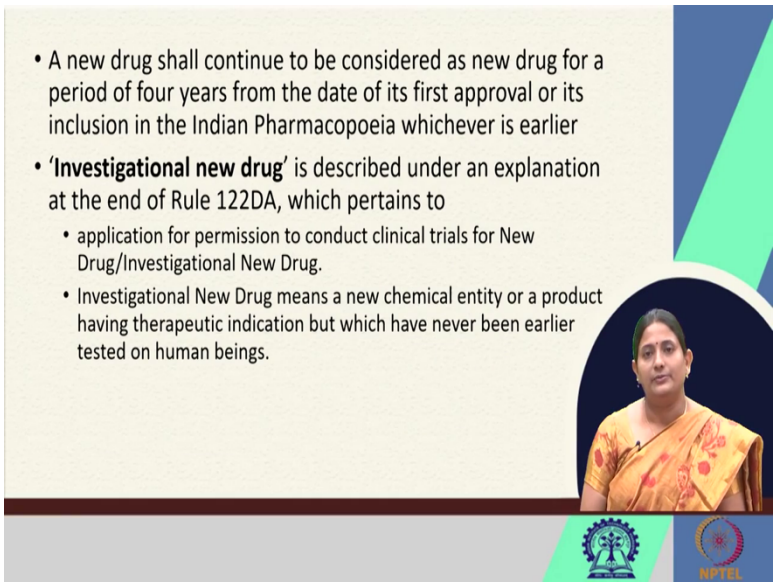

So, in this lecture I would like you to introduce certain concept. So, later when we will move to the biopharmaceuticals that would be helpful for you to understand the whole process. So, a ‘new drug’ is which has never been approved or which is now approved for the new drug indication.

But in India, there is a clause that a new drug shall continue to be considered as a new drug for a period of four years from the date of its first approval or its inclusion in the Indian Pharmacopoeia which is earlier. So, even though a drug is marketed or approved for marketing in India, the drug would be considered as a new drug till four years from the date of its first approval.

So, that four year becomes the exclusive period. So, the four year becomes the exclusive period during which it is again considered as the new drug molecule. So, for a new drug as we have already seen, before any drug molecule is introduced, first it has to be tested for safety and efficacy studies means how safe it is for the human being to use or how efficacy is the drug molecule.

So, how do we judge that? We get that information by the results of the clinical trials. So, it is again another regulatory approval that is required before any probable drug molecule or drug candidate is tested for the clinical trial. So, those are known as the investigational new drug or the IND. So, the investigational new drug is again described in an explanation to the rule 122DA.

So, the IND or the investigational new drug pertains to the application for permission to conduct clinical trials for the new drug or the investigational drug molecules. And basically, the IND means a new chemical entity or a product having therapeutic indication, but which have never been earlier tested in human beings.

So, now, to test those therapeutic molecules on human beings, we need certain permissions from the drug controller general or the CDSCO, Central Drugs Standard Control Organization of India and this is known as the IND or the investigational new drug.

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So, if we look into our Drugs and Cosmetic Act then we can find that in India, the drugs can be classified into different categories. Like first, drugs not yet approved in India, but it is approved elsewhere so, it may be possible in some country, some drug molecule has already been approved, but it has not been approved so far in India.

So, in this case, an applicant has to submit the clinical study results and the other published report regarding the studies with respect to the drug molecule and the results of the pharmacokinetics and the pharmacodynamics studies and all this data which is available before the safety and efficacy of the drug and that has to be submitted to the authority.

And second category which drugs approved in India within 4 years of the first approval of the same molecule. So, suppose already one drug molecule is approved and the same or nearly similar molecules are again or the same or it is approved in some country and now, that has been introduced in the India.

So, if it is already been marketed in India and if some other company is trying to apply it within the next 4 years, then in that case, we really do not need all the clinical trial data's only the BE data that is bioequivalence data is required that means they have to show that the drug molecule is nearly similar to the or is similar in with respect to their functioning to the earlier approved drug molecule.

And drug approved in India after 4 years of the first approval of the same molecule. So, if something has been already approved and some other company is trying to apply for the same drug molecule after the; after 4 years of the first approval, then again only the proof of the chemical equivalence is required not all the studies.

So, there are different set of requirements for the drug molecules depending on which state or depending what is the application is all about. So, this is about categorization of the drug as if something has been approved or not approved.

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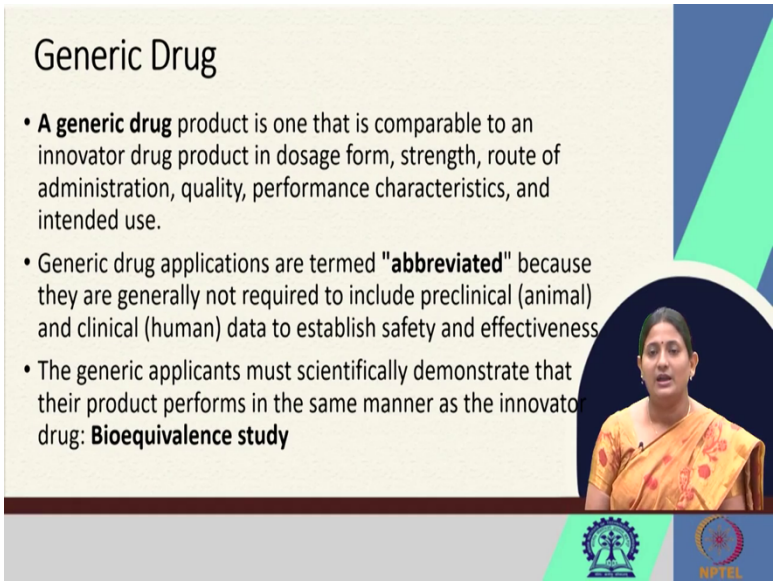

There are few other terminologies with respect to the drug molecule in India like one is the new drug as defined in the Act or sometimes it is known as the NCE- New Chemical Entity, another popular terminology which all of you might have heard is the generic drug. So, what is a generic drug?

So, a generic drug is a product which is really comparable to the innovator drug molecule. So, when drug molecule is introduced for the first time, it is known as the innovative drug product. A new substance or new molecule which has never been introduced for treatment of a particular indication.

So, if somebody develops a kind of a drug molecule which is nearly comparable to that drug molecule or the innovator drug molecule in terms of the dosage form, in terms of the strength of the medicine or the route of administration, quality, performance

characteristics and the intended use purpose, then that molecule can be called as the generic drug molecule.

And since this generic drugs are nearly comparable to the innovator drug molecule, the application for the generic drug molecule is sometimes known as the abbreviated application. So, if somebody applies for a new drug molecule that application is called as the NDA or the new drug application, but if someone applies for the approval for a generic drug molecule, then it is known as the abbreviated new drug molecule or the ANDA application.

So, what happens? What is the major difference between this new drug application or abbreviated new drug application? So, basically in the abbreviated new drug application, the data requirements are in the terms of safety and efficacy, or clinical data requirements are not that stringent or that adjustive as compared to the innovator drug molecule.

For an innovator drug molecule, you need to submit the preclinical data as well as the force like the clinical trial data and for the generic drug applications generally, the manufacturer does not have to submit the preclinical data like- the animal studies and also you know in many cases, they do not really required to study or to submit the human clinical data to establish the safety or efficacy.

Rather, what the generic company has to provide is the scientific evidences to show that the applied product is nearly similar to the innovator drug molecule. So, means it functions as if it is a new drug molecule or the innovator drug molecule which is known as the bioequivalence study or the BE study. So, those equivalence data are required for the generic drug molecule in the ANDA, ANDA application procedure which is very different from the innovator drug molecule procedure.

So, this is one of the important concepts which we keep on hearing. So, you might have heard that the generic drugs are really cheaper than the innovator drug, the reason being for the innovator drug molecule they have to perform lot many studies animal, human and the R&D process also involves certain cost. So, that is why in generally, the innovator drug molecules are priced higher.

On the other hand, in case of generic drug molecules, since the manufacturer does not have to submit the clinical trial data which is again very time consuming as well as the costly process. So, comparably the price of this generic molecules are low. So, that is one of the important thing which all of you should know.

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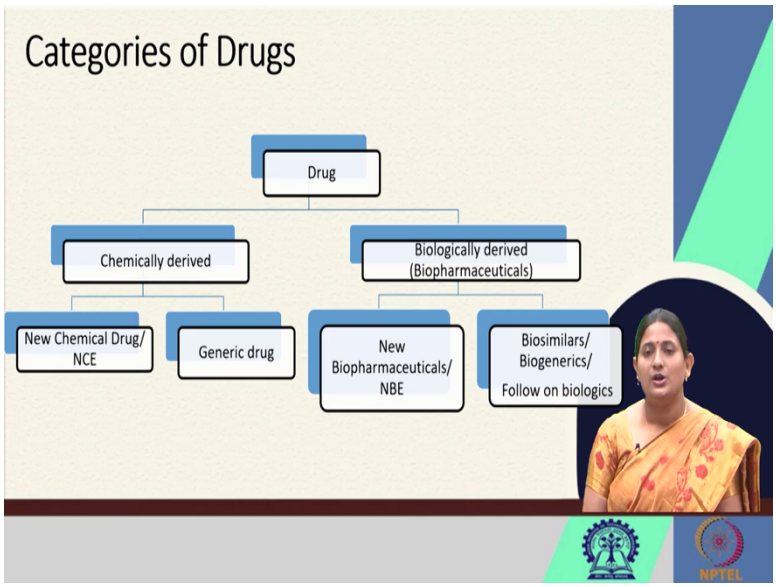

So, now broadly we will see the whole categorization of the drug molecule. So, the drug as defined in our Act or anywhere in the world, the drug molecule can be majorly of two types, first a drug substance which is chemically derived. So, chemically derived again, it may be from normal chemical synthesis process, or it may be derived from the plant sources.

So, this chemically derived molecule if it is used for the first time for a new indication or as we defined in the new drug definition, then it is known as the new chemical drug or the NCE. This NCE application process is known as the NDA, New Drug Application process and if it is already approved and the generic molecule or the similar molecule is now being applied, then it is known as the generic drug application which is generally applied through the ANDA procedure; Abbreviated New Drug Application procedure.

The other category of the drug is biologically derived drug. So, initially the Drugs and Cosmetic Act defined the new drug only, which is majorly this chemically derived, but as the recombinant DNA technology was available and number of drug molecules have been developed from the technology, then this lead to the categorization of the new drug

category which is the biologically derived drug molecule or otherwise known as the biologicals or biopharmaceuticals.

So, it includes everything which has been derived either by the use of the recombinant DNA technology or by any living microbial organisms like vaccines or any blood related product, different proteins or antibodies so, it includes a lot of thing.

And again, similarly like the chemically derived drugs, the biopharmaceuticals are also divided or can be divided into two parts, first new biopharmaceutical entities or the NBE which is again for new indications and the other one is the biosimilars or bio generics which is popularly also known as the follow on biologics. So, this is the equivalent of the generic drug for the biopharmaceuticals.

So, in case of the biopharmaceutical generics, we are, we call this generics for the biopharmaceutical drugs as bio-generics in India, we call it as biosimilars and in many other countries, it is known as the follow on biologics as well. Why there is different nomenclature? Because if you compare the generic drugs with the bio generic, there are two different kind of molecule.

First of all, the biopharmaceuticals are really very large and complex molecule protein structures where the structure of the protein, the size of the protein, their stability everything is highly variable and dependent on many factors and it is very difficult to produce. On the other hand, the chemically derived drugs are very easy to produce in comparison to the biopharmaceuticals.

And so, while we say that for the abbreviated new drug application or for the generic drug application, we do not need the clinicals trial data or the other animal study data only bioequivalence study data is enough. For the biopharmaceuticals or the follow-on biologics, the requirement are not that simple because these are protein molecules.

A slight difference in the shape or the size or the structure or even the way it has been stored may lead to number of changes in the drug molecule and that may lead to severe effect on the functioning of the efficacy of the drug molecule. Therefore, before a biosimilar is approved, the data submission requirements are quite complex in comparison to the generic drug molecule.

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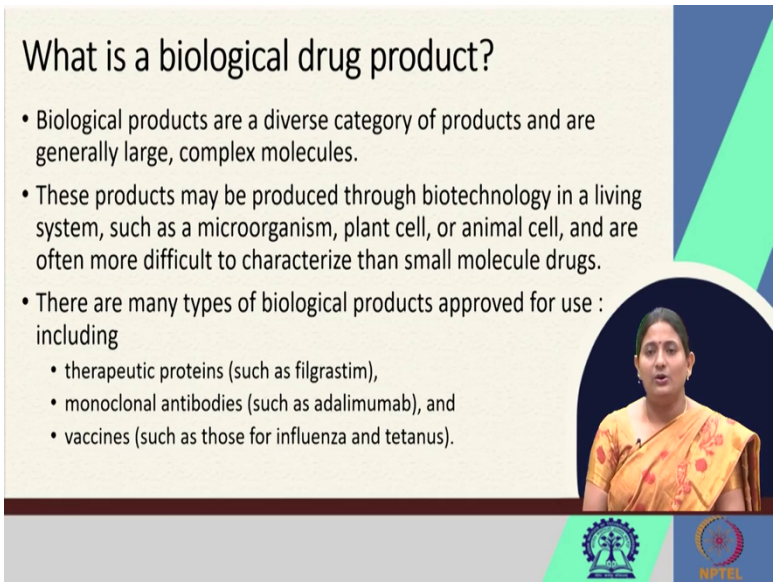

Now, worldwide if we look into the definition of the biological drug products, we will see that the biological drug products are diverse category of the products, and they are very large and complex molecules. And they may be produced through the processes involved in the biotechnology in a living system maybe, microorganisms or a plant cell or an animal cell and they are very difficult to characterize than the small drug molecules.

So, there are a number of biological molecules which has been approved in India as well as worldwide. So, like the therapeutic protein such as filgrastim, monoclonal antibodies, different vaccines for influenza, tetanus and now, this corona virus vaccine is one of the recent examples for this biological drug product.

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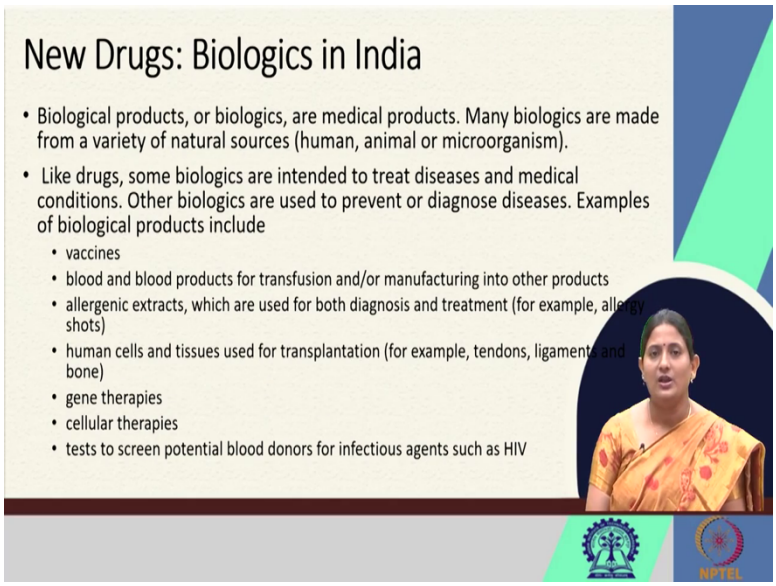

So, in India, the biological drug product or biologics is again coming under the category of the new drug. In India generally, all the recombinant DNA derived product or all the vaccines are generally regarded as new drug unless there are certain other conditions.

So, they are like generally derived from the living organism and if we see the biologics which are used for prevention or diagnosis of the disease, may include vaccines or blood related product or blood products required for the transfusion or manufacturing into the other products, allergenic extract which are used for both the diagnostic and the treatment purpose. Then human cells or the tissue which is used for transplantation, gene therapy products, cellular therapy products, tests to screen potential blood donors for the infectious agent such as HIV. So, all these also come under the purview of the biologics.

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And as I mentioned, the generic version of the biologic is called as the biosimilar. So, a biosimilar is a biological product which is highly similar and has no clinically meaningful difference from the existing approved reference product. So, now, even though there may be minor differences in the shape or size of the product, but the difference should not result in clinically significant difference. So, if the two drugs molecules acting, similarly on the same disease in the same way, then they may be considered as the biosimilars.

And it is generally regarded that the biosimilar should be highly similar to the reference product or the first innovator drug. So, a manufacturer who is developing a biosimilar should demonstrate that the product is highly similar to the reference product. Reference product mean the first product or the innovator drug molecule to which we are comparing. And these how do you know a certain that it is highly similar?

So, the characterization of the structure and function of both the reference product as well as the proposed biosimilar must be studied in depth so that it gives an idea that both of them are highly similar. So, similarity in terms of the purity, in terms of the chemical identity and in terms of the bio activity of the compounds in those case only it is regarded if they are found to be highly similar, then they only then they are considered as the biosimilar.

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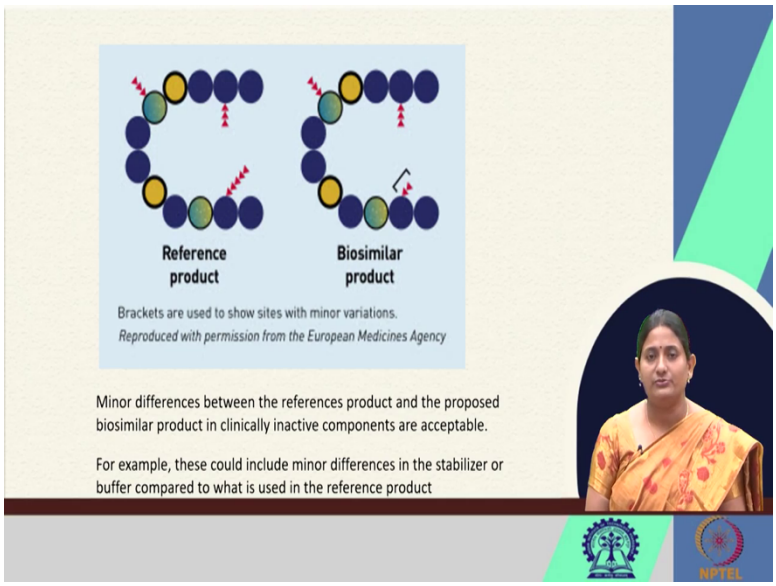

So, this is one of the examples which I have taken from the US FDA site. So, just to show you the difference between how the reference product or the biosimilar product may be similar or different. So, if you see these are a polypeptide chain or a protein molecule which has number of amino acid in it, but again, they might have different glycosylation structure means how the different glucose molecule or any other side chains are attached to the protein, main protein chain

so, there might be certain differences on how these protein molecules are different moieties, attached to the main protein molecule. Even though there is a structural difference, minor structural difference, but still they perform in the same way because majority of the structures are same. So, this has to be analyzed chemically and other by using sophisticated high-end technology like HPLC's, spectrophotometer or there are many NMR, there are many other like- how to study the three-dimensional structure of the protein.

So, there has been a lot of development in the technologies used for ascertaining the chemical, manufacturing or other characterization of the protein molecule. So, that has to be take taken care of and they should establish the similarity. So, here, the two products have minor differences between the stabilizing effect by the side chain. But still they are considered as the same or the biosimilars might be considered.

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Hence, the term, the biosimilar molecule should be highly similar to the reference molecule, and it should not result in significant chemical clinical meaningful differences. So, how do that is; how the manufacturers demonstrate that?

So, a manufacturer should demonstrate that the proposed biosimilar product is same in terms of the safety, purity and potency of the drug and it is demonstrated through the human pharmacokinetic studies that is the exposure studies to the human as well as the pharma; pharmacodynamic studies that is the various response studies. And they also assess the clinical immunogenicity of the product and if required, additional clinical studies are also performed.

So, this actually comprises a lot of studies for the simplification of the things. I am not going to the detailed of the studies which are applicable, but at least we should understand that the activity of the two-drug molecule, the reference as well as the biological drug molecule must be similar. So, the means we target must be same or the way it is acting must be same. So, those has to be ascertained.

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So, we have a reference drug product and now we have a biosimilar product. There is another category of the product which is known as the interchangeable product. So, these definitions are given more appropriately or more elaborately in the US FDA or in the EMA. So, I have taken the definitions from there so that you can understand. Even though we use these terminologies in India also, but it has not been defined in a proper way in any of our Act or the regulation.

For the simplification of the process, I am trying to describe you those definition which is generally used by the other drug regulatory authorities. So, the interchangeable product is a biosimilar product that meets the additional requirement which is outlined in one of the Act or legislation, which governs the biosimilar and other biologics. So, the legislation is known as the Biologics Price Competition and Innovation Act.

So, in that act, they have laid down certain provisions. So, the interchangeable product- if it meets those parameters, then it is known as the interchangeable product. So, what is that? So, the interchangeable product needs to show the same clinical result as the reference product.

So, in the biosimilar one, we said that there should not be meaningful differences in the clinical results, but here, it should be the same clinical result means. Whatever results the difference product is giving, the this interchangeable product also or should also give the same product same result.

And this interchangeable products can be changed if you want that medicines. So, if it is not available, the pharmacist may also give you the interchangeable product which will available to them, but in case of the biosimilar one, you need a doctor's prescription to see whether this would be same or not. So, there are minor differences, but since it is a biological molecule so, those minor differences may also carry certain weightage.

And so, here in this interchangeable product, for the products administered to a patient more than once, the risk in terms of safety and reduced efficacy for switching back and forth between an interchangeable product and a reference product will be evaluated. Means you can interchangeably use the reference drug as well as this interchangeable product. So, the activity must be similar to that extent that the changing of those two medicines will not have any adverse effect on the health of the patient.

So, this is another highly similar or total similar kind of the drug as the innovator drug molecule. So, these are the basic name or terminologies which are used in the case of the biopharmaceuticals like as I mentioned. One is the biopharmaceutical itself, then we have the biosimilars and we have the interchangeable products. So, they have been defined depending on the nature of product.

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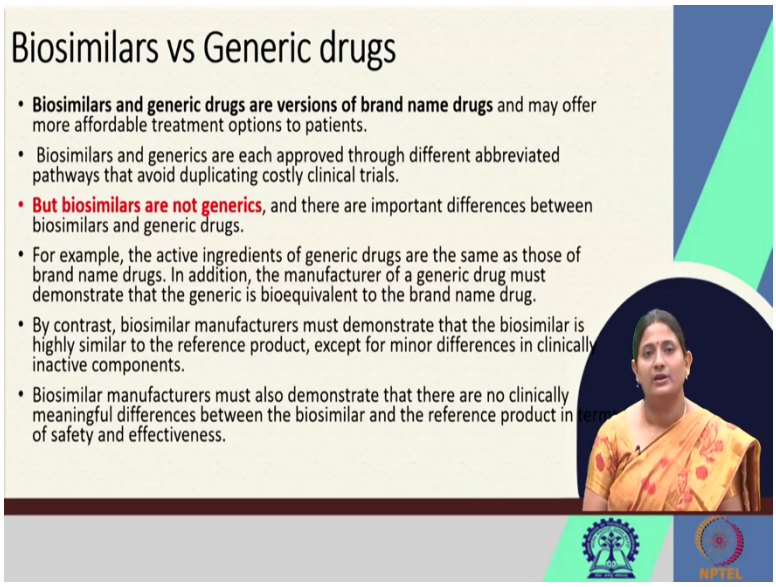

Now, if we compare the difference between a biosimilar as well as a generic drug, then in a general sense, we may say that the biosimilars and the generic drugs are the versions of the brand name drugs and they generally provide more affordable treatment option to

the patient. As I said the generic medicines are generally considered cheaper because depending on the regulatory requirement for the approval process. So, they are just an alternate or alternate version of the treatment.

And now, the pathway to this biosimilar or the generic drugs are different and they are known as the abbreviated pathway because it basically tries to avoid duplicating the clinical trial process which is very costly as well as the time consuming. Because both the molecules have to be proven and are already been proved similar and so, there is no need of carrying out the lengthy clinical trials which may take 5 to 10 years of time period.

So, they are approved to this abbreviated pathway. But one thing is that all the biosimilars are not generics, there are differences between the biosimilars as well as the generic molecule. For example, the active ingredient of a generic drug is the same as those of the brand name drug.

So, if it is a chemical substance or a chemical drug molecule so, the active drug molecules means the main acting component should be the same in case of the new drug as well as in the generic drug and in addition to that, the manufacturer of the generic drug must demonstrate that the generic is bioequivalent to the brand name drug or the innovator drug.

However, in case of these biosimilars, the manufacturers of the biosimilar drugs must demonstrate that the biosimilar is highly similar to the reference product, except minor differences in clinically inactive components. So, as I showed in the earlier picture, though it may have the main protein moiety as the same, but have minor differences in the side chains which is known as the inactive ingredient. So, that is allowed, but it may not be completely same.

And the biosimilar manufacturers has to demonstrate that there are no clinically meaningful difference between a biosimilar and the reference product in terms of safety or the effectiveness, it is acting in the same way as the main innovator drug is acting.

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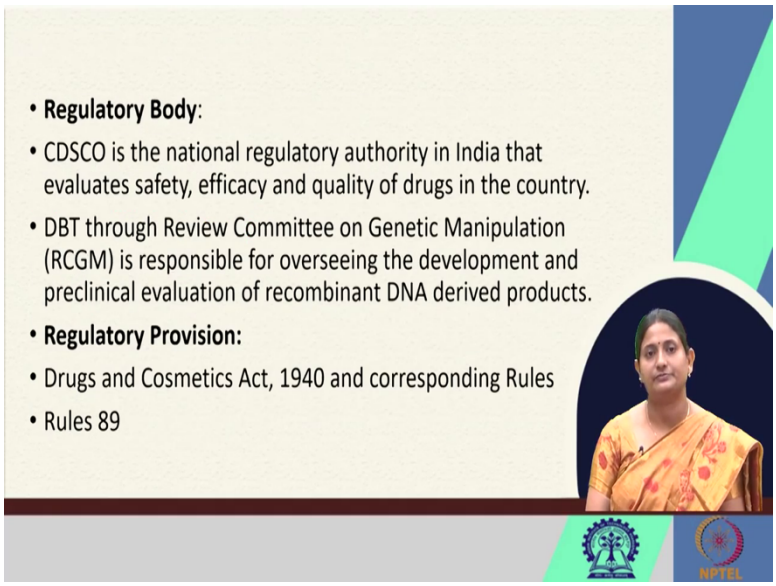

Now, let us come to the regulatory process. How these drug molecules are regulated in India? So, first let us discuss about the India. So, in India, all the drug products are regulated under the CDSCO or the Central Drugs Standard Control Organization. So, it is the apex body which is chaired by the DCGI Drug Controller General of India. So, the CDSCO is the national regulatory authority in India and it is the authority which evaluates the safety, efficacy and the quality of the drug in the country.

So, any drug which has to be manufactured in the country or which has to be imported or exported in the country from the other country should be regulated by the CDSCO. And as we have seen in our earlier discussion so, it is not only directly governed by the DBT, it is also governed through the other agencies like in the department of biotechnology. The department of biotechnology is involved through the two committees that is the review committee on the genetic manipulation or the RCGM which is basically our committee which is as we know it is an approval in nature.

So, this RCGM is responsible for overseeing the development and the preclinical evaluation of the recombinant DNA product; means all the permission for the animal studies and the protocol approval everything has to be done by the RCGM.

And in the later stages, GEAC, this Genetic Engineering Appraisal Committee is also involved which we will see. So, basically these two are the main bodies, then other agencies are also involved. And, the Drugs and Cosmetic Act of 1940, the corresponding

rules and Rule 89 of the environment protection authority is also applicable to the approval process for the drug molecule.

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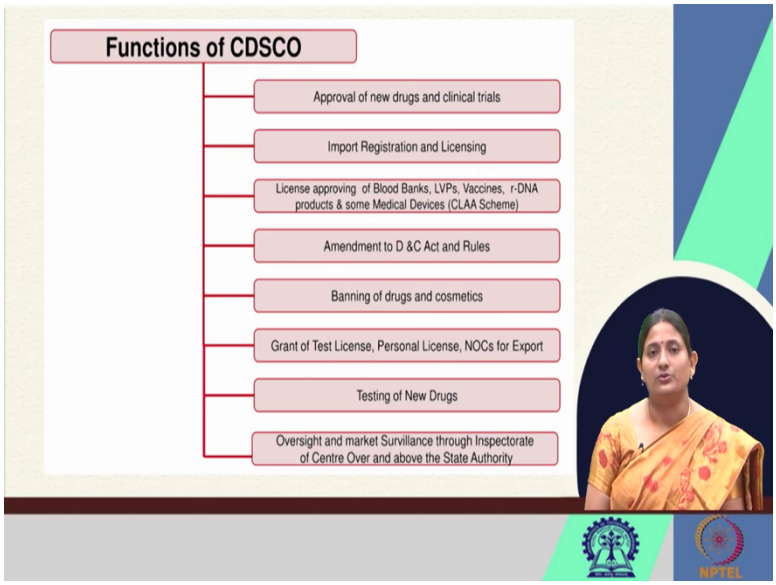

So, this CDSCO is basically the apex or the neural agency which approves the new drugs and gives approval for the clinical trials. It regulates the import registration and licensing is also issued by the CDSCO. Then license approving for the blood banks or vaccines, or r-DNA products and other medical devices are also given by CDSCO. Then, all the amendments to the Drugs and Cosmetic Act are done by this agency.

If some drugs are spurious or is not meeting the expected labelling or packaging requirement, then it also have the power, the power to ban those new drugs. It grants the test license, personal licenses and no objection certificates for the exports. Test of the new drug is also allowed or is given approval by the CDSCO.

Then, basically it oversees at the all the drug procedures, market surveillance with the inspection of the centre and it also regulates the state regulatory authority. So, the CDSCO has a number of functions which overall regulates the drug approval process in India.

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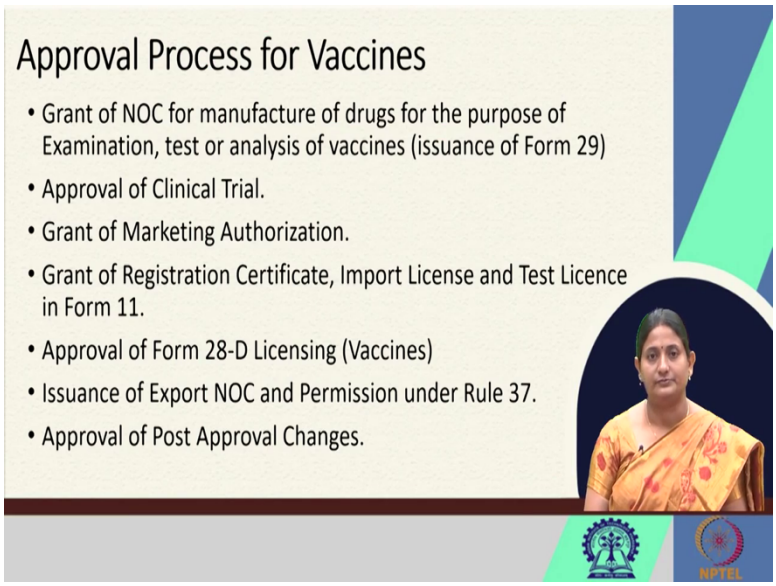

So, I would request you all to visit the CDSCO site as, they are developing more in the website. So, if you see we have different categories of the products. So, we have vaccines, we have r-DNA products, we have new drugs, normal chemical drugs. So, for each of these drugs, we have different forms and different regulatory requirement and that has to be approved.

So, just to show you, for example, if someone applies for the vaccine to manufacture vaccine in India, they have to take first the NOC for the manufacturing of the drug for the purpose of the examination test or analysis of the vaccine, then they have to get the approval for the clinical trials, then they will get the marketing authorization certificates, then the registration of the certificate, import license or other test license, then final approval and then, if they want to export, they need to again get NOC for the export procedure and if there are any changes, then for that also we need post approval changes.

So, this is the general process or general requirement for the different stages of the production or marketing or export of the drug molecule. Similarly for the recombinant DNA drug product also, we need to have the same procedure like need to have the grant of NOC for the examination test or analysis of the product, approval for the clinical trials, then the approval for the marketing authorization, then certificate for the registration, then final approval for the production and marketing, then export.

So, this is the basic hierarchy or the structure, generally through which the process takes place. And but again, it is a very lengthy process and there are various submission requirements to this process which has to be submitted and then, those submissions has to be reviewed by a specific agency whether it is IBSC or RDGM.

And there are certain technical advisory committees or different committees are also set up by the CDSCO depending on the individual cases and then, they approve the drug molecule as applied by for different stages.

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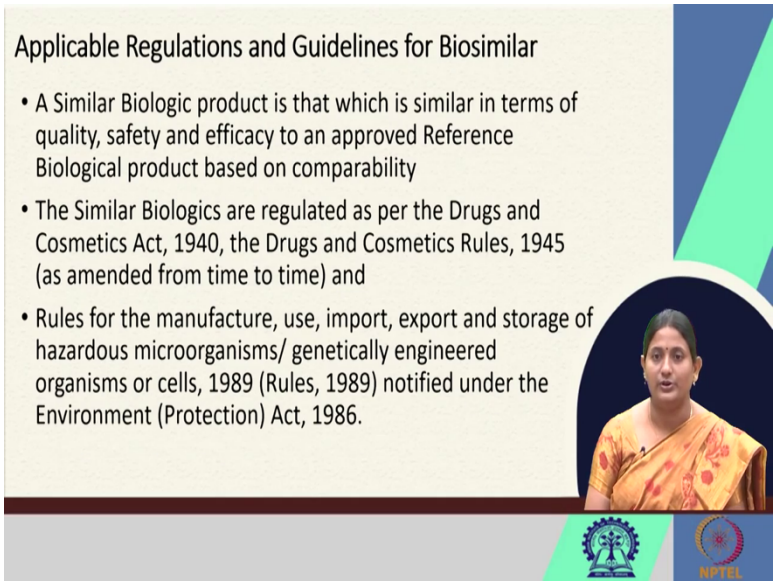

So, apart from the Drugs and Cosmetic Act and the Rule 89, the process which I just mentioned is for the new drug means we have to give the clinical trial data and everything has to be given. But if you want to apply for a biosimilar drug in India, there are other guidelines or other legislation also, in addition to the Drugs and Cosmetic Act and Drugs and Cosmetic Rule of 1945 which is amended from time to time and also, the Rule 89 is also applicable for the similar biologics.

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Beside those, we have the recombinant DNA safety guidelines of 1990, then we have the guidelines for generating the preclinical or clinical trial data for the rDNA vaccines or diagnostics in the biologicals of 1999 and then the CDSCO has also issued certain guidelines in the year 2008 for the submission requirements means what kind of dossier or documents has to be submitted for the biosimilar approval or in general, for a new drug.

So, there are specific documentation for submission of clinical trial application for evaluating the safety and the efficacy, requirement for the permission of the new drug approval, then what are the submission requirements for the post approval changes in the biological product means where you have to put the quality, safety and efficacy data.

Then, guideline regarding the preparation of the quality information for the drug submission for the new drug as well as the biotechnological as well as the biological drug product. So, specific guidelines have also been issued for the manufacturers so that that helps them in preparing the dozier in a proper manner so that the time taken for the review of this application can be minimized or it can be streamlined.

And also, we have certain guidelines developed by the department of biotechnology like guidelines and handbooks for the Institutional Biosafety Committees or IBSCs in 2011. Because you know wherever a drug molecule or recombinant drug molecule is produced,

they have to first constitute an Institutional Biosafety Committee. Now, that would be a nodal point where it will communicate with the other agencies like RCGM or GEAC.

And then, the DBT has also given thw guidelines on the similar biologics which is known as the regulatory requirements for the marketing authorization in India. So, first was issued in 2012, then this guideline is revised and in 2016, additional guideline for the biosimilars has been issued by the department of biotechnology.

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So, these are the guidelines which are required. So, if we see the whole approval process for the r-DNA pharmaceutical products, the major authorities which are involved in the approval process are the IBSC that is the Institutional Biosafety Committee, RCGM recombinant committee on genetic modification, GEAC Genetic Engineering Appraisal Committee, DCGI or the director general of Drug Controller General of India of CDSCO. So, these are the four authorities or four bodies which play a critical role in the approval process.

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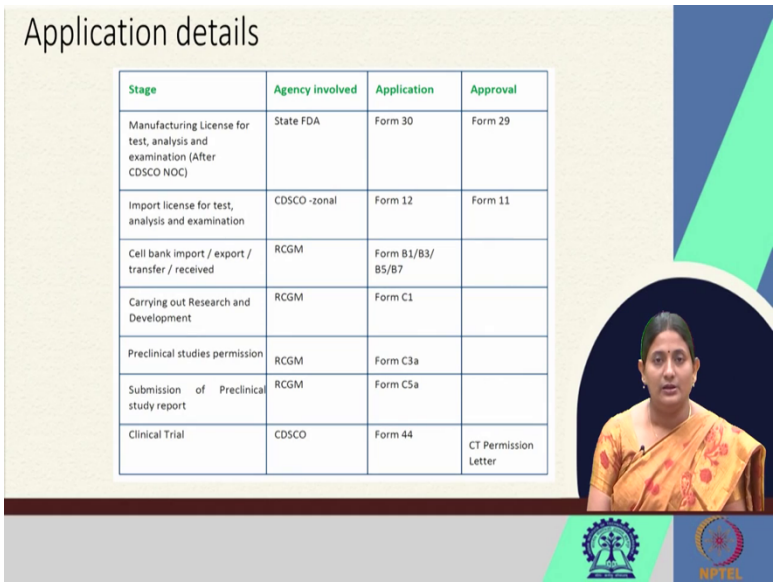

So, this is just to show you the various application requirement. So, there are number of forms which need to be filled up by the manufacturer and accordingly, they would get the approval in a different format. So, this is just to show you ok for like for manufacture license, for the test and analysis of the examination so, we need to where to apply like we have to apply to the State FDA or the CDSCO so, those has been given.

So, the application process is wholly online in the CDSCO portal. A portal known as the ‘Sugam portal’ where the online application for the drug molecules can be submitted and the manufacturers can create a login credential for themselves. Accordingly, there are number of helpful guidelines available to the manufacturers and as per that thing, they can submit the regulatory requirements.

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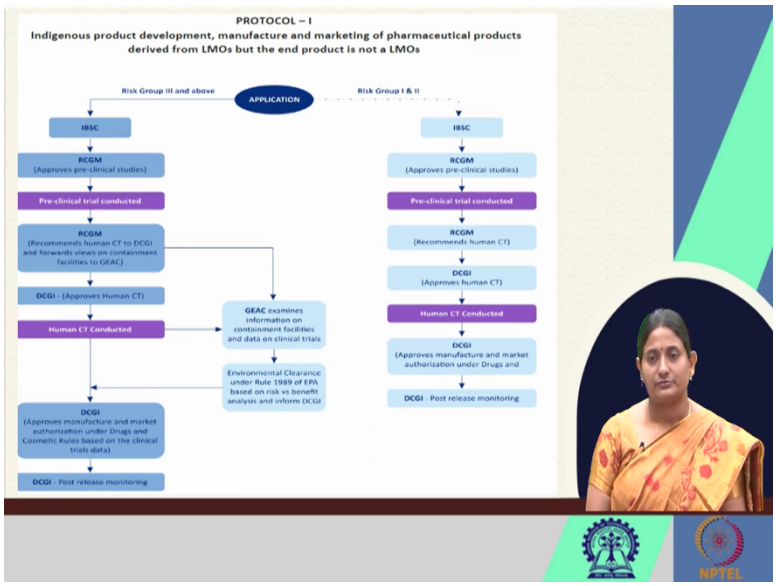

So, now there have been so, since the recombinant DNA technology has evolved, the number of deliberation is happened and they have tried to streamline the process how the recombinant drug molecule can be approved easily in India without delay in the time. So, for that, number of as I said like deliberations has been taken place.

So, one of the important report was Mashelkar committee report. There in that report, they have given five different pathways through which generally the drug approval takes place depending on the nature of the product. So, this one is taken from that Mashelkar committee report and also, you can get it from the biological biosimilar guidelines.

So, accordingly they have given five protocol. So, when the application is for a product development, manufacturing and marketing which is derived from a living modified organism and the end product is not a living modified organism, derived from the biotechnological process, the end product is not a LMO.

In that case, depending on the nature on the type of the microorganism used, they have classified the application into two ways. So, if you see the other guidance, they have classified the risk categories so, we have risk group of I and II which are lower risky microorganism and then, higher risk category microorganism this III and above.

So, if any drug molecule is derived from a lower risk category like risk group I or II group of microorganisms. Then first the IBSC Institute Biosafety Committee sends the

protocols to the RCGM or review committee on the genetic manipulation for the approval of the preclinical studies. Once it gets the approval from the RCGM, then the preclinical trials are conducted and those results are further submitted to RCGM again for the approval of the human clinical trials, if the data are satisfactory.

And RCGM is a satisfied of the protocol, then it recommends for the human clinical trial where the application goes to the DCGI and finally, the DCGI approves. So, DCGI is the authority for the approval of the human clinical trials and the DCGI approves after that data has been submitted, human clinical trial data the DCGI finally, approves the drug for the manufacture and marketing in India. And that post-release of the drug the DCGI; DCGI itself is the monitoring authority. So, this is for the risk group I or II which is the lower risk category.

But if a drug molecule is produced from the higher risk category of the organisms, then another step is involved during the human clinical trial phase. So, what happens? Then there comes the rule of the GEAC, Genetic Engineering Appraisal Committee. So, once the RCGM approves or sends the application for the recommendation of the DCGI, the GEAC examines the information and the containment facilities and the data on the clinical trials also tries to make out the different risk associated to the environment.

Because you know the GEAC is basically the body which is constituted under the mandate of rule 89. So, they basically look the data from the perspective of the environmental link angle. And if that is approved by the GEAC, then after both the DCGI is satisfied with the data for proceeding of the human clinical trial and GEAC also gives a nod, then only final approval for the marketing and the commercialization of the drug molecule is given by the DCGI and then, DCGI again takes the charge of the post drug monitoring.

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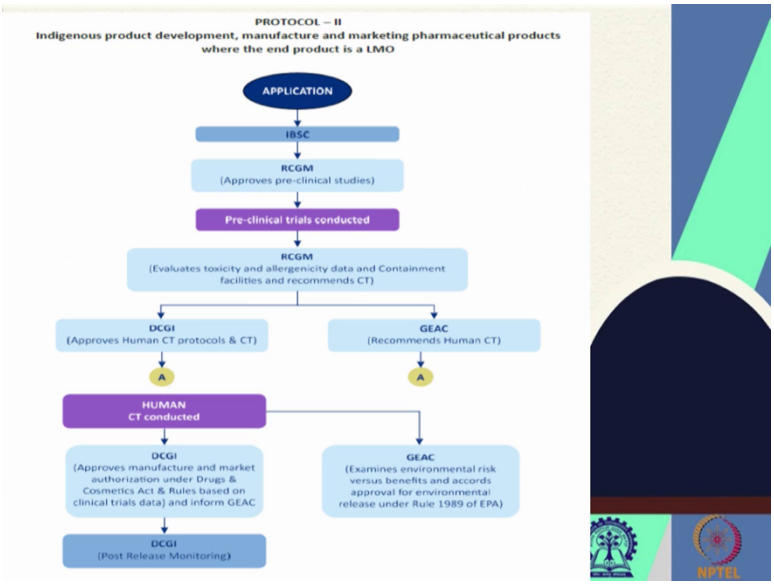

Similarly, in the second protocol, we have the product development manufacturing and marketing. Where the end product is not an LMO- living modified organism. So, here also, the same process IBSC sends the application to the RCGM for the approval of the preclinical studies, once the preclinical trials are conducted, the RCGM evaluates the toxicity and the allergenicity data and the containment facilities and recommends for the clinical trial and the clinical trial is approved for the DCGI and the GEAC.

And so, if it is satisfied, the human clinical trial is conducted and further evaluated by both GEAC and DCGI and the final product is approved for the marketing.

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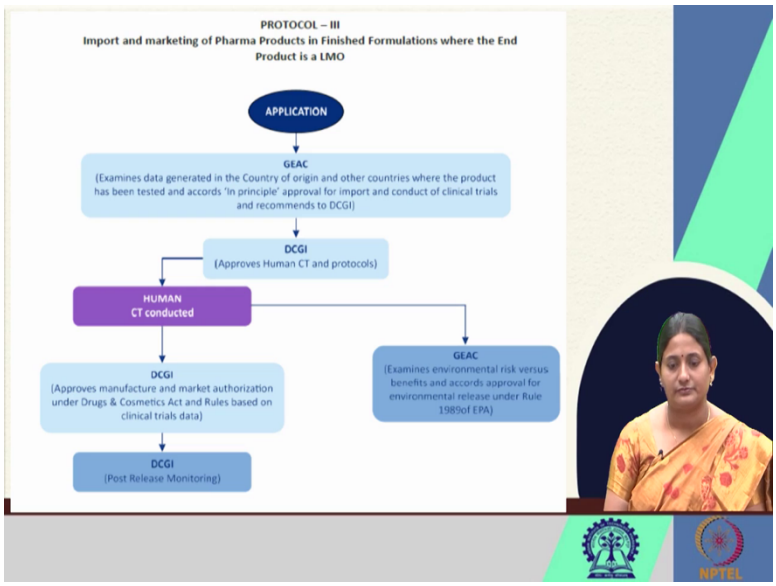

Third protocol is the import and marketing of the pharmaceutical products in finished formulations where the end product is an LMO. So, when it is for import and the drug molecule is imported, then here first the application is checked by the GEAC. So, the GEAC, what it does?

It examines the data generated by the country of origin and other countries where the product has been already tested and approved and then, it gives the approval for the import of those medicines, pharmaceutical product and allows for the clinical trial which which will be recommended by the DCGI.

So, after getting the nod of GEAC, the DCGI approved for the human clinical trials and looks into the proposal for the human clinical trial protocol and then, the human clinical trial is conducted and those data are further scrutinized by the DCGI and the final when it is conducted in India. Though GEAC also check the risk associated to the environment and then, the risk versus benefit has to be compared under the rule of 1989 and then finally, they drug is approved.

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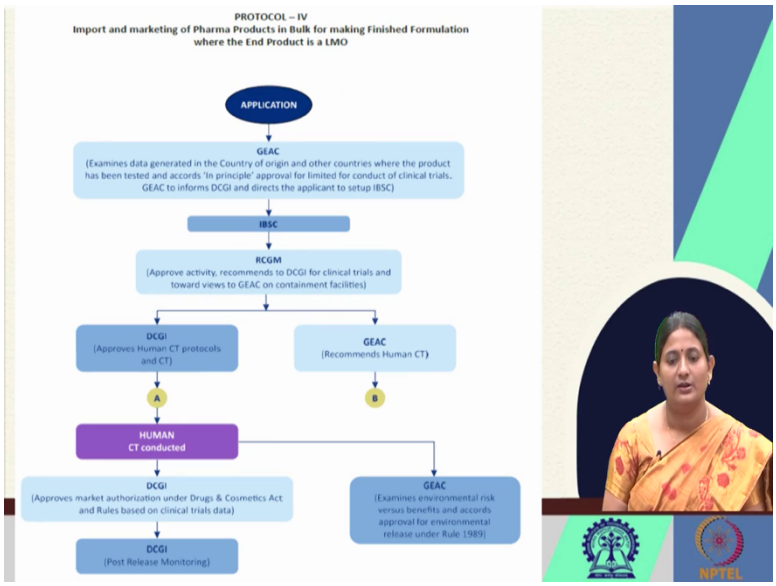

Similarly, does it have another protocol for the import and marketing of the pharma products in bulk for making the finished formulations where the end product is an LMO. So, in the same way, it is also the same, how it is approved like both the drugs after getting the nod of GEAC, it is again given back to the IBSC because again, it has to be a converted into a finished pharmaceutical product IBSC send.

So, the first procedure again comes into picture IBSC again goes to RCGM for the recommendation of the preclinical and clinical trials and then, the clinical trials are approved by DCGI and GEAC and finally, the nod are given by the both the agency.

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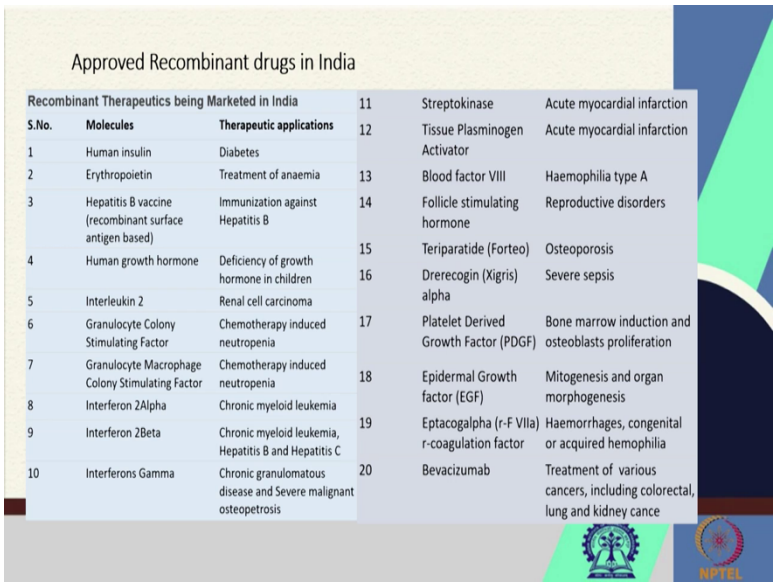

So, these are just a list of few examples. There are nearly 40 or more drugs has been approved by the Indian drug CDSCO, Central Drugs Standard Control Organization. So, these are just a tentative list of recombinant DNA factor; DNA molecules which are approved for various elements. So, India is a progressing fast in this direction and India is also known as in hub for the biosimilars, but we have certain differences with respect to the other countries in terms of stringency required for the data.

So, where India is trying to cope up with the other developed nations, and trying to adopt different guidelines as given by the international organization or as followed by the US FDA or European Medical Agencies. So, we are trying our best to have good quality of the biopharmaceutical products where the manufacturing standards, the purity and the safety of the drugs are at the best quality so that it can give a proper treatment to the patients.

So, this is all about in brief the biopharmaceutical approval process in India and hope you have got a little bit of idea about the whole process in India. So, I will also try to give you a little bit snaps out of the US FDA in the next lecture. So, thank you for being in this lecture. So, see you in the next one.

Thank you.